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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,575	02/09/2001	Thomas J. Kodadek	UTSD:566US/SLH	1617

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EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,575	KODADEK, THOMAS J.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-30* is/are pending in the application.

4a) Of the above claim(s) *2,6,16-21 and 24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,10-15,22,23 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment and submitted certified Rule 132 Declaration dated 11/9/04 and 11/18, respectively are hereby acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 1-7 and 10-30 are currently pending.

Claims 2, 6, 16-21, 24-29 are withdrawn from further consideration as being drawn to a nonelected invention

Claims 1, 3-5, 7, 10-15, 22-23 and 30 are under consideration.

Election/Restriction

Applicant's election, without traverse, of Group I (claims 1-15, 22-26 and 29-30) in the applicant's correspondence dated May 19, 2004 was acknowledged in the prior office action. Accordingly, claims 16-21, 27-28 and 31-39 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Applicant's further election of species which read on claims 1, 3-5, 7-15, 22, 23 and 30 is again acknowledged

Accordingly, claims 2, 6, 16-21, 24-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

2. This application contains nonelected claims 2, 6, 16-21, 24-29. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objection (s) and/or Rejection (s)

Applicant's arguments were considered and deemed persuasive resulting in the withdrawal of the indefinite rejection of claims 1, 3-5, 7-15, 22-23 and 30 under 35 U.S.C. 112, second paragraph in item 6. of the previous office action.

The Rule 132 Declaration by Thomas Kodadek was considered and deemed persuasive to overcome:

a. the anticipation rejection of claims 1, 3-5, 7-15, 22-23 and 30 under 35 U.S.C. 102(a) as being anticipated by Zhang et al., Nature Biotechnology Vol. 18 (Jan. 2000) pages 71-74; and

b. the anticipation rejection of claims 1, 3-5 and 7-15 under 35 U.S.C. 102(a) as being anticipated by Zhang et al., Current Biology (3/12/99) Vol. 9: 417-420

in items 8 and 9 of the prior office action.

Applicant's amendment has resulted in the withdrawal of the following previous rejections:

a. the rejection of claims 1, 3-5, 8-11, 22 and 23 under 35 U.S.C. 102(b) as being anticipated by Jappelli et al. J. Mol. Biology (1996) Vol. 259: 575-578;

b. the rejection of claims 1, 3-5, 8-11, 22, 23 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jappelli et al. J. Mol. Biology (1996) Vol. 259: 575-

c. the rejection of claims 1, 3-5, 7-11, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Jappelli et al. J. Mol. Biology (1996) Vol. 259: 575-578 and Watt et al. US Pat. No. 6,610,495 (8/03: filed 1/99 or earlier); and

d. the rejection of claims 1, 3-5, 8-15, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Jappelli et al. J. Mol. Biology (1996) Vol. 259: 575-578.

Response To Applicant's Arguments

Regarding the Jappelli et al. reference applicant argues that this reference is limited in its teaching to screening folded, intact proteins or peptides domains as the library screen target, whereas the presently claimed invention addresses linear peptide of 8-15 residues. This argument was not found persuasive.

Initially, it is noted that the Jappelli reference does not make a distinction between "folded" vs. "linear" targets as alleged by applicant; and as such applicant is failing to consider the reference teaching as a whole which would be the applicability of the Jappelli reference method to screen peptides of any size (e.g. amino acid length) or conformation (linear, folded or otherwise).

Regarding, the '495 and '561 patents cited in the prior rejections (e.g. as secondary references) applicant argues that these patent references fail to teach the use of small linear peptides selected from target proteins as binding partners. This argument was not found persuasive.

The rationale for citing the '495 and '561 patents was not to address the use of small linear peptides in the Jappelli reference method but for the rationale clearly recited in the previous rejections. Additionally, in response to applicant's arguments against the

references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

New Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 103

3. Claims 1, 3-5, 10-15, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jappelli et al. J. Mol. Biology (1996) Vol. 259: 575-578 in view of Murray et al. US Pat. No. 6,365,347 (4/04: filed 4/98 or earlier) and Dostmann et al., Pharmacol. Ther. Vol. 82, No's. 2-3, pages 373-387 (1999) taken separately, or in combination.

The present claims are directed to a method for identifying a peptide-peptide interaction comprising:

(a) providing a 1st fusion construct comprising a "target peptide" of 8-15 residues fused to a "1st DNA binding domain (DBD)";

(b) providing a 2nd fusion construction comprising a "library encoded peptide (LEP)" fused to a "2nd (DBD)", wherein the binding domains work as a complex to facilitate binding of the domains to a "prokaryotic operator region";

(c) contacting said 1st and 2nd fusion constructs in a "prokaryotic host cell" comprising an operator operationally linked to a coding region for "one or more indicator polypeptides"; and

(d) determining binding of said complex to said operator region.

It is noted for purposes of claim interpretation, that there is no functional or sequence means of distinguishing between what one classifies as a "target peptide" as compared to a "library encoded peptide (LEP)" with the sole exception of sequence length (e.g. "target peptide" must possess 8-15 amino acid residues). These terms are not defined in the specification.

It is also noted that the term "library encoded" with regard to the phrase "library encoded peptide" represents a product-by-process limitation which is not afforded any patentable weight. In this regard, any peptide may result from the screening of a peptide library and/or is capable of being synthesized as one member of a plurality (e.g. 2 or more) or library of peptide compounds; and to do so is an obvious matter of design choice to one of ordinary skill in the art.

It is further noted that claiming (e.g. claims 12-15) preferred binding affinities (e.g. 10^{-3} to 10^{-6}) is an inherent feature regarding the compounds screened and as such is not afforded any patentable weight whatsoever. Absent preselecting compounds have known binding affinities, the binding affinity of an unknown compound in the presently claimed assay is inherent to the compound e.g. the unknown compound may not bind at all or may be a "tight" binding compound.

Japelli teaches a "method for identifying a peptide-peptide interaction" (e.g. enzyme-protein inhibitor complex (cyclic adenosine monophosphate dependent protein kinase (cAPKcs) as a model: e.g. or "protein-protein recognition" or "protein-peptide interactions: see e.g. page 575, left column) utilizing a lambda repressor reconstitution assay comprising:

(a) providing a 1st fusion construction comprising a "target peptide" (e.g. PKI: 20 amino acid: 5-24 and mutants thereof) fused to a "1st DBD" wherein the binding domains work as a complex to facilitate binding of the domains to a "prokaryotic operator region" (e.g. see Figure 1, especially 1B and page 577, left column: "interaction between the kinase and high affinity peptide inhibitor, which serves to dimerize the repressor");
(b) providing a 2nd fusion construct comprising a "library encoded peptide (LEP)" (e.g. alpha isoform of the human cAPKcs e.g. amino acids 6-350) & a "2nd DBD" (e.g. amino acids 1-102) (e.g. see page 576, Fig. 1, especially Fig. 1(A));
(c) contacting said 1st and 2nd fusion constructs in a "prokaryotic host cell" (e.g. bacterial cell: E.Coli i.e. strain Q537) comprising an operator operationally linked to a coding region for "one or more indicator polypeptides" (e.g.see Table 1 description of E. Coli strain Q537) with fusion "under control of the lac promoter" (e.g. see Fig. 1); and
(d) determining binding of said complex to said operator region elicited by cotransformants expressing receptor fusions being resistant to lamba infection (e.g. see page 577 and Table 1). The Japelli reference teaches (e.g. page 575 and page 577, left column) the presence of a prokaryotic operator region (e.g. operationally linked to one or more indicator proteins) and the role of the DNA binding domain's dimerization to effect repressor reconstitution.

The Japelli reference also teaches the use of a lamba repressor reconstitution assay to generate lambda infection resistant mutants with binding affinities of:
a. 1.6×10^{-9} M (wild type PKI (6-22))
b. 1.74×10^{-8} M (Tyr 10 peptide analog)

c. $4.25x10^{-7}$ (Phe10Ala mutant).

Additionally, the Japelli reference further provides explicit motivation to make further competititve enzyme (e.g. alpha isoform of the human cAPKcs) inhibitors; including the use of a random peptide library in order to further screen additional clones for binding in order to discover more phenotypes or to select rare phage resistant variants. See page 577, left to right column.

Although teaching the use of "target peptide(s)" of **20 residues** which are peptide inhibitors of cAPKC's, the Japelli reference method differs from the presently claimed invention by failing to teach the use of "target peptide(s) of **8-15 residues"**.

However, Murray et al. teach recombinantly producing libraries of peptide inhibitors of biological pathways for use as diagnostic/therapeutic agents, especially library peptides ranging from **4-16** amino acids (e.g. see col. 5, especially lines 15-25) and peptide inhibitors of kinases, including cAPKcs. See Abstract; patent claims 1-16; figures (especially figures 8a and8b); examples (especially examples 1-5); col. 2, 7-10.

Similarly, Dostmann et al. describe screening peptide library inhibitors of cyclic AMP-kinase wherein the peptides are of length **8-14** amino acid residues and the subsequent screening to discover "tight" binding peptides e.g. GRTGRRNAI (9 amino acid) peptide to cAMP-kinase binding affinity of $0.073x10^{-6}$. See Abstract; page 375, right column-left column of page 376; 378-381; Figures 1-3; Tables 1-4.

One of ordinary skill in the art at the time of applicant's invention would have been motivated to utilize "target peptide(s) of 8-15 residues" for screening instead of the Japelli 20 residue peptide inhibitors since even Japelli recognized the importance of

making inhibitors of cAPKC's; and both the Murray and Dostmann references provide further motivation to make shorter peptide libraries (e.g. @ 8-15 residues) for screening prospective cAPK's inhibitors for their diagnostic/therapeutic use.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Japelli reference method to utilize "target peptides of 8-15 residues in order to screen for prospective competitive inhibitors of 8-15 residues for their diagnostic/therapeutic use.

4. Claims 1, 3-5, 10-15, 22, 23 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jappelli et al. in view of Murray et al. US'347 and Dostmann et al., as applied to claims 1, 3-5, 10-15, 22 and 23 above, and further in view of Peters et al. US Pat. No. 6,214,561 (3/01: filed 11/97).

The teaching of the Jappelli et al. reference in view of Murray et al. US'347 and Dostmann et al. described above is hereby incorporated; and although, the Japelli reference teaches "assessing binding of the target peptide to the library encoded peptide", (as in determining binding e.g. inhibition constants: e.g. see page 577 both columns) the Japelli reference differs from the presently claimed invention (e.g. claim 30) by failing to explicitly teach "assessing binding of the target peptide to the library encoded peptide by use of Western blot, mass spectroscopy (MS) or nuclear magnetic resonance (NMR)".

Peters et al. teach that Western blot (e.g. see col. 1, especially lines 40-50), mass spectroscopy (e.g. MALDI: see col. 2, especially lines 25-30) represent "common

methods" to screen libraries for determining target/ligand binding. Additionally, the Peters et al. reference teach a preferred NMR technique for determining target/ligand binding. E.g. see col. 3-6; patent claims 1-19.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize routine screening protocols (E.g. western blot/MS/NMR) as taught by the Peters et al. reference for Aassessing binding of the target peptide to the library encoded peptides of the Japelli reference as a matter of design choice with a reasonable expectation of success.

5. Claims 1, 3-5, 7, 10-15, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jappelli et al. in view of Murray et al. US'347 and Dostmann et al., as applied to claims 1, 3-5, 10-15, 22 and 23 above, and further in view of Watt et al. US Pat. No. 6,610,495 (8/03: filed 1/99 or earlier).

The teaching of the Jappelli et al. reference in view of Murray et al. US'347 and Dostmann et al. described above is hereby incorporated by reference in its entirety.

Although, the Japelli reference teaches the utilization of an E. Coli. host with a lac promoter containing an operator operationally linked to "one or more indicator polypeptide" the Japelli reference fails to teach the use of B-gal as an indicator polypeptide in its peptide-peptide lambda repressor reconstitution assay.

However, Watt et al. teach methods for modulating "protein-protein" interactions involving "reconstitution of a functional transcription factor leading to expression of the reporter molecule" (e.g. col. 6) including protein-protein dimerization involving DNA-

binding domains (e.g. see col. 7) in which host cell expression preferably employs E. Coli , lac (lacz) promoter and an operator linked to beta-galactosidase as the Apreferred reporter molecule≅ (e.g. see col. 12-13).

Accordingly, one of ordinary skill in the art would be motivated to modify the Japelli reference method expression system (e.g E. Coli), as modified by Murray and/or Dostmann references, to further utilize beta galactosidase as an indicator polypeptide in light of the Watt reference teaching of the preferred use of such an indicator polypeptide in protein-protein DNA binding dimerization assays analogous to the Japelli reference method.

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Japelli reference E.coli expression system to select beta galactosidase as a reporter molecule in light of the Watt et al. Reference teaching that such a reporter is preferred

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

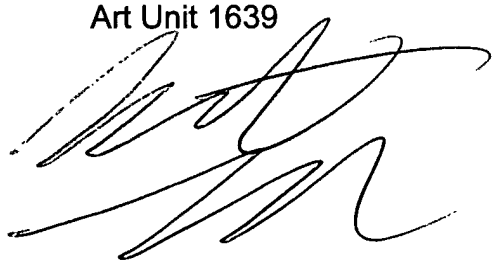
Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639



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January 31, 2005